



Implications of overweight in gastric cancer: a multicenter study in a Western patient population

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► To cite this version:

J. Kulig, M. Sierzega, P. Kolodziejczyk, J. Dadan, M. Drews, et al.. Implications of overweight in gastric cancer: a multicenter study in a Western patient population. *EJSO - European Journal of Surgical Oncology*, 2010, 36 (10), pp.969. <10.1016/j.ejso.2010.07.007>. <hal-00625558>

HAL Id: hal-00625558

<https://hal.science/hal-00625558v1>

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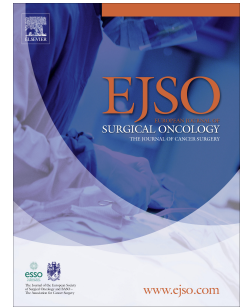


HAL Authorization

Accepted Manuscript

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PII: S0748-7983(10)00312-4

DOI: [10.1016/j.ejso.2010.07.007](https://doi.org/10.1016/j.ejso.2010.07.007)

Reference: YEJSO 3025

To appear in: *European Journal of Surgical Oncology*

Received Date: 18 March 2010

Revised Date: 10 July 2010

Accepted Date: 19 July 2010

Please cite this article as: Kulig J, Sierzega M, Kolodziejczyk P, Dadan J, Drews M, Fraczek M, Jeziorski A, Krawczyk M, Starzynska T, Wallner G. Implications of overweight in gastric cancer: a multicenter study in a Western patient population, *European Journal of Surgical Oncology* (2010), doi: 10.1016/j.ejso.2010.07.007

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Title: Implications of overweight in gastric cancer: a multicenter study in a Western patient population

Short Title: Overweight and prognosis in gastric cancer

Article type: Original research article

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Keywords: gastric cancer; overweight; body mass index; lymph node dissection; prognosis; postoperative complications

ABSTRACT

AIMS: The purpose of this study was to evaluate the effects of overweight on surgical and long-term outcomes in a Western population of patients with gastric cancer (GC).

METHODS: An electronic database of all patients with resectable GC treated between 1986 and 1998 at seven university surgical centres cooperating in the Polish Gastric Cancer Study Group was reviewed. Overweight was defined as a body mass index (BMI) of 25 kg/m² or higher.

RESULTS: Four hundred and ninety-two of 1992 (25%) patients were overweight. Postoperatively, higher BMI was associated with higher rates of cardiopulmonary complications (16% vs 12%, $P=0.001$) and intra-abdominal abscess (6.9% vs 2.9%, $P<0.001$). However, other complications and mortality rates were unaffected. The median disease-specific survival of overweight patients was significantly higher (36.7 months, 95% confidence interval (CI) 29.0 to 44.4) than those with BMI<25 kg/m² (25.7 months, 95% CI 23.2 to 28.1; $P=0.003$). These differences were due to the lower frequencies of patients with T3 and T4 tumours, metastatic lymph nodes, distant metastases, and non-curative resections. A Cox proportional hazards model identified age, depth of infiltration, lymph node metastases, distant metastases, and residual tumour category as the independent prognostic factors.

CONCLUSIONS: Overweight is not the independent prognostic factor for long-term survival in a Western-type population of GC.

INTRODUCTION

Obesity is gaining increasing attention in surgical oncology. This is partially due to the recent epidemiological data suggesting that excess body weight is associated with an increased risk of various gastrointestinal malignancies, including gastric cancer, and particularly oesophagogastric adenocarcinomas.^{1,2} Moreover, from the surgical point of view, overweight patients are also exposed to a greater risk of interventions due to obesity-related comorbidities and increased incidence of postoperative complications. Another important aspect is related to some previous studies suggesting that overweight may influence the oncological outcomes of patients with gastrointestinal cancers.^{3,4}

Several authors have already reported that overweight increases the incidence of general and intra-abdominal complications in Asian patients undergoing gastrectomy for gastric cancer.⁵⁻¹² Some recent studies also suggested that obesity may correlate with long-term prognosis.^{9,13,14} However, as the prevalence of obesity is one of the principal differences between Western and Japanese or Korean patients with gastric cancer, influencing surgical technique and staging, simple approximation of observations reported from Asian populations is biased.^{15,16} This is particularly important for lymphadenectomy, as excess abdominal fat may markedly impair lymph node dissection and can play an important role in explaining the differences in surgical outcomes between Western and Asian patients. Surprisingly, data for the association between overweight and long-term outcomes outside of Japan and Korea is scarce. Moreover, the paucity of studies concerning Western populations and potential flaws in reports from single institutions or including only a limited number of patients preclude a reliable evaluation of existing data.¹⁷⁻¹⁹

The aim of this study was to examine the relationship between overweight and long-term survival of patients undergoing gastrectomy for gastric cancer and to evaluate the potential mechanisms underlying these effects in terms of postoperative complications and adequacy of surgical therapy.

METHODS

Patient selection

An electronic database of all patients with resectable gastric cancer treated between 1986 and 1998 at seven university surgical centres participating in the Polish Gastric Cancer Study Group (PGCSG) was reviewed. All relevant data, including demographics, clinical findings, details of surgical procedures and histopathological parameters, were collected prospectively using standard forms. Overweight was defined according to the World Health Organization classification as a body mass index (BMI) of 25 kg/m² or higher.²⁰ This study was approved by the Bioethics Committees at each institution.

Treatment and follow-up

The type of stomach resection was selected based on tumour location and was not influenced by patients' BMI. In general, a subtotal gastrectomy with Billroth II reconstruction was used for tumours of the distal and some middle stomach. Proximal gastric cancer without gross involvement of surrounding tissues was treated with a proximal subtotal gastrectomy and oesophagogastric anastomosis. Total gastrectomy with Roux-en-Y reconstruction was typically used in other cases. Primary tumours were resected *en bloc* with perigastric lymph nodes (groups 1-6 according to the Japanese Gastric Cancer Association (JGCA)), whereas extragastric nodal stations (groups 7-11 and/or 7-12, depending on the site of the primary tumour) were dissected separately. The extent of lymphadenectomy was described by the operating surgeon and finally evaluated by the pathologist by counting resected lymph nodes in individual stations as defined by the JGCA. Lymph nodes were identified and retrieved from surgical specimens without using any specific technique to increase nodal retrieval rate. Paraffin-embedded nodes were stained with haematoxylin and eosin, and examined microscopically for metastases. No special immunohistochemical techniques were used to

identify micrometastases. Follow-up data were collected based on clinical examination every 3-6 months after discharge and dates of death were verified using data obtained from the census registry office. Survival rates were calculated based on the disease-specific principle, i.e. deaths due to gastric cancer were accepted as complete observations, while death due to other reasons and lost to follow-up was considered as a censored observation.

Statistical methods

Mann–Whitney U and χ^2 tests were used where appropriate to compare the distribution of individual variables between groups. Survival data was analysed according to the Kaplan–Meier method and included postoperative mortality; the log rank test was used to detect differences between groups. Multivariable analysis was performed using a Cox proportional hazards model with a backward stepwise selection procedure. The probability for entering the model was 0.050 and that for removal from the model was 0.100. $P < 0.050$ was considered statistically significant. Statistical analysis was performed using the SPSS® version 16 software package (SPSS, Chicago, Illinois, USA).

RESULTS

Demographic data

Between 1986 and 1998, 1992 records with detailed information regarding patient-related and tumour-related variables, including body height and body weight, were identified in the PGCSG database. The median BMI was 22.7 (range 15 to 39) and 492 patients had BMI of 25 kg/m² or more. Table 1 shows clinico-pathological features of the analysed population.

Compared to patients with BMI <25 kg/m², overweight was associated with a slightly higher incidence of cardiocirculatory disorders and a significantly higher rate of diabetes mellitus.

Surgery

No significant differences were observed with respect to the type of gastrectomy, extent of lymphadenectomy, and the proportion of patients undergoing pancreaticosplenectomy.

There was a negative linear correlation between BMI and the number of dissected lymph nodes with a correlation coefficient $r = -0.072$ ($P=0.002$). Overweight patients had a higher proportion of cases with 15 or less nodes in the surgical specimen (45% vs 37%, $P=0.002$) and the correlation between this proportion and BMI was highly significant ($r=0.759$, $P<0.001$). The overall mean number of removed lymph nodes in our series was lower than currently accepted as a standard, but most patients analysed in this study were operated on before 1995, when a policy of routine extent of lymphadenectomy of at least D2 was implemented. Moreover, a limited lymph node dissection was generally performed in all patients with synchronous distant metastases. The following variables were tested by logistic regression analysis to identify those associated with an inadequate number (i.e. 15 or less) of dissected lymph nodes: patient age (< 40, 40-65, > 65 years), sex, BMI (continuous variable), tumour location (upper, middle, distal third, whole stomach), Lauren's type, depth of wall penetration (T category), nodal status (positive or negative), distant metastases (present,

absent), type of surgical resection, pancreaticosplenectomy, and extent of lymphadenectomy. D1 lymphadenectomy (Odds Ratio (OR) 4.16, 95%CI 3.12 to 5.54, $P<0.001$), absence of lymph node metastases (OR 2.13, 95%CI 1.64 to 2.75, $P<0.001$), tumours limited to the gastric mucosa and submucosa (OR 1.57, 95%CI 1.05 to 2.35, $P=0.027$), and BMI (OR 1.03, 95%CI 1.01 to 1.07, $P=0.033$) were independent predictors of low lymph node count in surgical specimens.

Pathology

The anatomical distribution of tumours within the stomach and the proportion of individual Lauren's types were similar between groups. Overweight patients had a significantly lower proportion of category T3 and T4 tumours (64% vs 71%, $P=0.005$) and the prevalence of synchronous distant metastases. Moreover, patients with a BMI below 25 kg/m² were significantly more likely to undergo non-curative resection.

Overweight was associated with a lower proportion of patients with metastatic lymph nodes (59% vs 70%, $P<0.001$) and a lower median ratio of metastatic/resected lymph nodes (0.17 vs 0.30, $P=0.003$). For both of these parameters there was a significant negative linear correlation with BMI and corresponding Pearson's coefficients of regression were -0.730 ($P=0.003$) and -0.075 ($P=0.007$), respectively. However, if 16 or more lymph nodes were dissected, the proportion of patients with individual N categories was unaffected by BMI and there was no correlation between BMI and the prevalence of metastatic lymph nodes or the ratio of metastatic/resected lymph nodes.

Postoperative course

Postoperative recovery was uneventful in 1277 patients and morbidity rates for overall complications were similar regardless of BMI (Tab. 2). Overweight was associated with

significantly higher rates of cardiopulmonary complications (16% vs 12%, $P=0.010$) and intra-abdominal abscess (6.9% vs 2.9%, $P<0.001$). Other complications and mortality rates were not influenced by BMI. The median postoperative stay was longer in overweight subjects (17 vs 14 days, $P<0.001$).

Long-term survival

At the time of final follow-up (December 2006), 1295 of 1992 patients had died, and the median follow-up period for surviving subjects was 104 months. The median disease-specific survival of overweight patients was significantly higher (36.7 months, 95%CI 29.0 to 44.4) than those with $BMI<25\text{ kg/m}^2$ (25.7 months, 95%CI 23.2 to 28.1; $P=0.003$) (Fig. 1). To explain these differences, survival rates between overweight and non-overweight patients were compared after stratification based on tumour staging. Since Kaplan-Meier's curves for groups with $BMI<25\text{ kg/m}^2$ and $\geq 25\text{ kg/m}^2$ superimposed on stages I-II and III-IV (Fig.2A-B), survival benefits of overweight were related to the differences in tumour staging.

A Cox proportional hazards model was constructed including variables that significantly affected disease-specific survival in the univariate analysis, i.e. age (<40, 40–65, >65 years), BMI ($<25\text{ kg/m}^2$, $\geq 25\text{ kg/m}^2$), tumour location (upper, middle or distal third, whole stomach), Laurén's classification (intestinal, diffuse, mixed), depth of infiltration (T1-T4), nodal status (N0-Nx), metastatic/resected lymph node ratio (0, 0-20%, >20%), distant metastases (no, yes), potentially curative resection (no, yes), splenectomy (no, yes), and postoperative chemotherapy (no, yes). The only independent prognostic factors were age, depth of infiltration, lymph node metastases, metastatic/resected lymph node ratio, distant metastases, and residual tumour category (Tab. 3). The hazard ratio in overweight patients compared to those with $BMI<25\text{ kg/m}^2$ was 0.89 (95% CI 0.77 to 1.04, $P=0.139$). Considering the differences observed among tumour stages, two additional Cox models were constructed for

stages IA through II and separately IIIA through IV. Nevertheless, overweight was not a significant predictor of survival with hazard ratios of 0.940 (95%CI 0.703 to 1.257, $P=0.667$) and 0.916 (95%CI 0.777 to 1.079, $P=0.292$), respectively. Similar results were obtained if the model was stratified for curative and non-curative resections.

DISCUSSION

The influence of overweight on survival

One of the major clinical differences between patients with gastric cancer in the West and those in Japan or Korea is a much higher prevalence of overweight and obesity that may have important practical consequences. The most important aspect is related to findings from Japanese populations suggesting that obesity may correlate with long-term prognosis of gastric carcinoma. Tokunaga et al.¹⁴ presented the largest analysis to date evaluating the correlation of BMI and long-term survival in 7925 patients treated with curative intent in a Japanese centre. Unexpectedly, the 5-year survival rate of 84.0% in overweight patients (BMI ≥ 25 kg/m²; n = 1126) was significantly higher ($P < 0.001$) than 76.7% in the non-obese group (BMI < 25 kg/m²; n = 6799). Moreover, multivariate analysis of potential prognostic factors demonstrated that higher BMI significantly reduced the risk of death (hazard ratio 0.874, 95% CI 0.773-0.988, $P = 0.032$). Despite these results, prognostic implications of overweight are not well established for gastric cancer as smaller Japanese studies demonstrated that high BMI was an independent predictor of recurrence⁹ or questioned its influence on the long-term outcomes.^{8, 10, 12, 21} Similarly, the definitive implications of overweight in Western patients with gastric cancer have yet to be determined due to the paucity of data for the association between BMI and prognosis.²²

Using a well defined multi-institutional data set from a Western country, the present study demonstrated that overweight was associated with a significant survival benefit by univariate analysis. However, unlike Tokunaga et al.,¹⁴ BMI ≥ 25 kg/m² was not an independent prognostic factor, suggesting that other covariates are responsible for such findings. The three most relevant aspects of overweight that may influence patients' survival are the relationship

between BMI and postoperative mortality, tumour staging, and adequacy of surgical therapy, discussed below.

Correlation of BMI with postoperative complications

Most previous retrospective studies from Asian populations suggest that BMI influences the occurrence of surgical complications in gastric cancer surgery indirectly by increasing operation time^{8-10, 12} and blood loss^{8-10, 23}, but also directly increasing rates of pancreatic fistula⁶⁻⁸ and abdominal abscess.^{8, 24} Moreover, these observations are supported by the results of randomized clinical trials confirming the detrimental effects of overweight.^{5, 25} Although some reports from Western populations revealed that BMI was not a significant predictor of postoperative morbidity^{18, 19}, the present findings strongly suggest that overweight may significantly contribute to the early postoperative outcomes. However, as in other reports, high BMI did not increase mortality rates, and thus cannot be responsible for the marked differences in long-term survival rates.

Implications of overweight for lymph node dissection

Inadequate lymph node dissection during gastrectomy could be another factor potentially worsening a patients' prognosis, as excess fat may limit accessibility to lymph nodes located deep in the adipose tissue around major abdominal vessels not included in the routine *en block* resection. Such assumptions are based on several observations concerning the different extent of lymphadenectomy.^{5, 9, 21, 23} However, previous reports from Western population-based databases and randomized clinical trials provided no data on the influence of BMI on the likelihood of undergoing adequate lymph node assessment.^{15, 26-29} In the present study, BMI significantly affected the proportion of patients with 15 or less lymph nodes removed and after stratifying patients for the extent of lymphadenectomy, this effect was preserved for both

D1 and D2 dissection. As several reports emphasised the importance of the stage migration phenomenon and poorer prognosis related to inadequate lymph node dissection, including our series (hazard ratio for Nx 1.85, 95%CI 1.48 to 2.32, $P < 0.001$), this observation has important clinical implications for surgeons operating obese individuals.

Impact of BMI on tumour staging

Staging differences related to BMI may be another potential factor responsible for discrepancies in long-term survival between overweight and non-overweight patients. Present findings suggest that high BMI is associated with markedly reduced proportions of tumours infiltrating gastric serosa, surrounding organs, metastatic lymph nodes, and distant metastases. As these variables are most commonly reported as independent prognostic factors for gastric cancer, the most likely explanation of better long-term survival found in the univariate analysis for overweight in our population is the correlation between BMI and tumour staging. This hypothesis is confirmed by the Kaplan-Meier's plots and Cox's proportional hazards models stratified for the American Joint Committee on Cancer (AJCC) stage (Fig.2A-B). Data collected in a Japanese cohort of 7925 patients suggested a similar conclusion that the prevalence of T3-4 and N2-3 cancers decreases significantly in patients with BMI ≥ 25 kg/m².¹⁴ Nevertheless, these correlations should be further validated with population-based databases since some studies involving smaller Asian populations failed to confirm any association between BMI and staging.^{8, 10, 12} Moreover, the mechanism of such less aggressive behaviour of gastric cancer in overweight individuals is yet to be determined, as some previous studies in hormone-dependent cancers (breast and prostate) and colorectal cancer reported a positive correlation between BMI and cancer stages, unlike the results of this study.³⁰

Conclusion

The present study provided for the first time data for the association between BMI and prognosis of gastric cancer from a large-scale Western-type population. Although higher BMI increased rates of some postoperative complications and impaired adequacy of lymph node dissection, better survival rates observed in overweight patients were related to the higher proportion of less advanced tumours. Therefore, overweight was not an independent prognostic factor for long-term survival.

AUTHORS' CONTRIBUTIONS

Study concept and design: Kulig, Sierzega, Kolodziejczyk.

Acquisition of data: Dadan, Drews, Frączek, Jeziorski, Kolodziejczyk, Krawczyk, Sierzega, Starzynska, Wallner.

Analysis and interpretation of data: Sierzega, Kolodziejczyk.

Drafting of the manuscript: Sierzega, Kolodziejczyk.

Critical revision of the manuscript: Dadan, Drews, Frączek, Jeziorski, Krawczyk, Kulig, Starzynska, Wallner.

All authors had access to portions of the raw data corresponding to their investigational sites.

Jan Kulig, Marek Sierzega, and Piotr Kolodziejczyk had access to all data in the study and analysis.

CONFLICT OF INTEREST STATEMENTS

The authors declare that they have no conflicts of interest.

ETHICS COMMITTEE APPROVAL

This study was approved by the Bioethics Committees at each institution.

ROLE OF FUNDING SOURCE

This study was financially supported by the Polish State Committee for Scientific Research, Grants no. 3 P05C 067 23p01, 2 P05C 024 29, 3 P05C 031 22, N403 069 31/3255

The funding source did not participate in study design, collection, analysis, or interpretation of the data, or writing of the report.

ACKNOWLEDGMENT

Other Members of the Polish Gastric Cancer Study Group:

Roman Bandurski, Andrzej Dabrowski, Halina Jaroszewicz-Heigelmann, Krzysztof Marlicz,
Wiktor Łaszewicz, Zbigniew Puchalski, Bolesław Stawny, Antoni M. Szczepanik, Jarosław
Szymczuk, Konrad Wronski

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TABLES

Table 1. Clinico-pathological features of overweight (BMI $\geq 25\text{kg/m}^2$) and non-overweight (BMI $< 25\text{kg/m}^2$) patients

	BMI $\geq 25\text{ kg/m}^2$ (n=492)	BMI $< 25\text{ kg/m}^2$ (n=1500)	P
Gender			0.510 [†]
female	161	467	
male	331	1033	
Age, yr (median (range))	59 (18-85)	60 (19-85)	0.298 [‡]
Co-morbidities			
cardiocirculatory	53	127	0.121 [†]
diabetes	18	24	0.006 [†]
Tumour location			0.126 [†]
upper	74	250	
middle	162	545	
distal	94	287	
whole stomach	162	418	
Laurén's classification			0.955 [†]
intestinal	266	824	
diffused	170	509	
mixed	56	167	
Depth of infiltration (AJCC 2002)			0.042 [†]
T1	68	159	
T2	109	280	
T3	218	714	
T4	97	347	

	BMI \geq 25 kg/m ² (n=492)	BMI<25 kg/m ² (n=1500)	P
Lymph node metastases (AJCC 2002)			0.005†
N0	86	225	
N1	61	246	
N2	70	272	
N3	54	200	
Nx*	221	557	
Distant metastases	112	460	0.003†
No. of lymph nodes (mean \pm SD)	13.5 \pm 10.3	14.7 \pm 10.1	0.028‡
Metastatic/resected lymph node ratio (median (range))	0.17 (0-1.0)	0.30 (0-1.0)	0.003‡
Type of gastrectomy			0.061†
subtotal distal	232	738	
total	214	670	
proximal	46	92	
Splenectomy	136	443	0.422†
Distal pancreatectomy	23	62	0.606†
Lymphadenectomy (JGCA)			0.273†
D1	147	398	
D2	163	491	
D2+	182	611	
Potentially curative resection (R0)	309	806	0.001†
Chemotherapy	256	841	0.151†

*15 or less lymph nodes removed; † chi-square test; ‡ U Mann-Withney test; BMI – Body

Mass Index; AJCC - American Joint Committee on Cancer; JGCA - Japanese Gastric Cancer

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Table 2. Postoperative complications according to BMI

	BMI \geq 25 kg/m ² (n=492)	BMI<25 kg/m ² (n=1500)	P*
Any complication	182	533	0.558
Cardiopulmonary	79	174	0.010
Anastomotic leakage	17	36	0.206
Intra-abdominal abscess	34	43	<0.001
Intra-abdominal bleeding	6	15	0.679
Wound infection	19	46	0.389
Other	15	60	0.306
Relaparotomy	23	57	0.391
Mortality	2	16	0.179

* chi-square test

Table 3. Multivariate analysis of independent prognostic factors for survival (Cox proportional hazards model)

Parameter	Category	Hazard Ratio (95%CI)	<i>P</i>
Age (years)	< 40	1	
	40–65	1.35 (1.04-1.76)	0.024
	> 65	1.69 (1.26-2.27)	< 0.001
BMI	<25 kg/m ²	1	
	≥25 kg/m ²	0.89 (0.77-1.04)	0.139
Tumour location	Distal	1	
	Middle	0.99 (0.87-1.21)	0.881
	Upper	1.13 (0.66-1.81)	0.894
	Whole	1.16 (0.62-2.15)	0.647
Laurén's classification	Intestinal	1	
	Diffuse	1.01 (0.87-1.16)	0.932
	Mixed	1.02 (0.84-1.25)	0.809
Splenectomy	No	1	
	Yes	1.09 (0.95-1.26)	0.232
Depth of infiltration	T1	1	
	T2	1.94 (1.35-2.78)	< 0.001
	T3	2.71 (1.92-3.83)	< 0.001
	T4	3.33 (2.28-4.88)	< 0.001
Lymph node metastases	N0	1	
	N1	1.32 (0.96-1.81)	0.085
	N2	2.59 (2.10-3.18)	< 0.001
	N3	3.54 (2.75-4.56)	< 0.001
	Nx	1.85 (1.48-2.32)	< 0.001
Metastatic/resected lymph node ratio	0	1	
	0–20%	1.45 (1.07-1.97)	0.018
	>20%	2.11 (1.67-2.65)	<0.001
Distant metastases	No	1	
	Yes	1.37 (1.13-1.66)	0.002
Residual tumour category	R0	1	
	R1 or R2	2.21 (1.99-3.5)	< 0.001

Adjuvant chemotherapy	No	1	0.583
	Yes	0.96 (0.83-1.11)	

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FIGURE LEGENDS

Fig. 1. Disease-specific survival for overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$) and non-overweight ($\text{BMI} < 25 \text{ kg/m}^2$) patients ($p = 0.003$, log-rank test).

Fig. 2. Disease-specific survival for overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$) and non-overweight ($\text{BMI} < 25 \text{ kg/m}^2$) patients according to tumour stage. **A.** Stage I and II ($p = 0.960$, log-rank test); **B.** Stage III and IV ($p = 0.229$, log-rank test)

